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Oncology Treatment Discovery

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September 2023, Volume 1, Issue 2

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http://ojs.bbwpublisher.com/index.php/OTD

Observation on the Effect of Interventional Devascularization in the Treatment of Liver Cirrhosis with Portal Hypertension

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Abstract: *Objective:* To analyze the clinical effect of interventional devascularization in the treatment of liver cirrhosis with portal hypertension. *Methods:* 80 patients with liver cirrhosis and portal hypertension admitted between January 2020 and January 2023 were selected as research subjects. They were divided into a control group (surgical devascularization) and an experimental group (interventional devascularization) through the computer grouping method, and the effect of the treatment received by both groups were compared. *Results:* (i) The efficacy of the treatment received in the experimental group was 94.87%, which was significantly higher than that of the control group, which was 76.92% ($P < 0.05$). (ii) There was no difference in the levels of alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) between the control group and the experimental group before treatment ($P > 0.05$); after treatment, the levels of ALT, AST, and ALP in the experimental group were statistically significantly lower than those in the control group ($P < 0.05$). (iii) Compared with the total complication rate of 28.21% in the control group, the total complication rate of the experimental group was lower at 10.25%, and the statistical significance was established ($P < 0.05$). *Conclusion:* Interventional devascularization has demonstrated positive outcomes in treating liver cirrhosis and portal hypertension. This is evident in the enhancement of liver function and its high safety profile. Consequently, it merits wider adoption and utilization in clinical practice.

Keywords: Interventional devascularization; Liver cirrhosis and portal hypertension; Liver function

Online publication: September 26, 2023

1. Introduction

When liver cirrhosis develops to a certain degree, a series of syndromes such as portal hypertension, hypersplenism, and ascites will occur due to establishment and opening of collateral circulation [1]. The establishment of collateral circulation usually occurs at the esophagus and gastric fundus, and the main clinical manifestation is varicose veins. Usually, portal hypertension is accompanied by upper gastrointestinal bleeding [2]. When the portal pressure increases, the collateral circulation between the portal vein and the vena cava expands. The treatment methods for cirrhotic portal hypertension include drugs, surgery, etc. The effect of surgical treatment is more ideal compared to conservative treatment, [3]. In this study, the efficacy of interventional devascularization in the treatment of cirrhotic portal hypertension was analyzed.

2. Clinical information and methods

2.1. Clinical information

A total of 80 patients with liver cirrhosis and portal hypertension treated between January 2020 and January 2023 were selected as research subjects. The patients were divided into a control group (surgical devascularization) and experimental group by the computer grouping method. Inclusion criteria: (i) diagnosed with liver cirrhosis by laboratory diagnosis, (ii) signed an informed consent, (iii) patency of the main portal vein. Exclusion criteria: (i) gastrointestinal hemorrhage on admission, (ii) infection in other body parts, (iii) has other serious malignant diseases, (iv) history of surgery. In the control group, there were 20 male and 19 female patients, with ages ranging from 33 to 65 years and an average age of 49.00 ± 4.66 years. In the experimental group, there were 20 male and 19 female patients, with ages ranging from 33 to 63 years and an average age of 48.00 ± 4.63 years. Statistical software was employed to compare the gender and age between the two groups of patients, revealing no significant differences ($P > 0.05$), indicating their comparability.

2.2. Methods

The control group was treated by surgical devascularization: the whole spleen was removed, and the blood vessels around the cardia and gastric fundus were blocked. Routine ligation of the gastric tubular vein branch was performed at 6 locations away from the lower end of the esophagus, and the high esophageal branch was cut off at the same time. Antibiotics and hepatoprotective drugs were routinely administrated after surgery.

The experimental group was treated by interventional devascularization: the patient was placed in the supine position on the angiography table, and the 21G Chiba needle was used to puncture the branch of the intrahepatic portal vein or the branch of the intrasplenic splenic vein through ultrasound guidance. The guide wire was inserted, and the puncture tract was properly expanded along the guide wire. Then, the catheter sheath was introduced into the portal vein. The blood pressure of the patient was then measured. A catheter was placed at the splenic hilum at the beginning of the splenic vein and the main trunk of the superior mesenteric vein, and digital subtraction angiography (DSA) was performed to observe the status of the portal vein and its collaterals. The femoral artery was punctured by the Seldinger technique, and the catheter was placed in the main trunk of the splenic artery near the splenic hilum, and splenic arteriography was performed. A suspension of contrast medium, gelatin sponge particles, and antibiotics were injected into the main trunk of the splenic artery through fluoroscopy until the blood flow of the splenic artery disappears. The embolism area was controlled between 50–80%. Angiography was performed again, and the embolism area was recorded. A guide was inserted into the proximal main trunk of the portal vein collateral vessel, and then DSA was performed to determine the direction and velocity of blood flow, followed by embolization treatment. If the blood flow velocity was high and the varicose veins had thickened with obvious branches, 5% morrhuate sodium or 99% absolute alcohol was injected through the catheter. Simultaneously, a spring steel ring was placed to embolize the proximal main trunk of the side branch vessels. After about 3 minutes, a contrast agent was injected to determine the degree of embolism until the distal end of the embolized varicose vein is no longer visible. Next, a catheter was inserted into the vein, and the portography was re-examined, and the free portal vein pressure was measured again after the intervention was cut off. The puncture channel was blocked by a spring steel coil or gelatin sponge, and the bleeding was stopped by extubation. Anti-infection, fluid replacement and other symptomatic treatment were routinely performed postoperatively.

2.3. Efficacy and observation indicators

2.3.1. Evaluation of efficacy

(i) Cured: symptoms and signs of the disease disappeared, imaging results were normal, and no varicose veins

were found by endoscopic examination. (ii) Markedly effective: symptoms and signs of the disease disappeared, imaging examinations indicated improvements, and no varicose veins were found during endoscopic examination. (iii) Effective: the signs and symptoms of the disease improved, but varicose veins were still visible through endoscopy. (iv) Ineffective: disease symptoms, signs, and imaging results only improved slightly or worsened, and endoscopic results showed obvious varicose veins [4,5].

2.3.2. Observation indicators

(1) Liver function indicators: 3 mL of venous blood was drawn in the morning on an empty stomach, centrifuged for 10 minutes, and the upper layer was extracted for testing. The levels of glutamic acid aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were detected by an automatic biochemical analyzer. (2) Complications: fever, rebleeding, infection of the surgical site, and lung infection.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 22.0. data related to efficacy and rate of complications of both groups were compared using a χ^2 test, while the liver functions were compared using a t-test. $P < 0.05$ indicated statistical significance.

3. Results

3.1. Treatment efficacy

The treatment received in the experimental group demonstrated significantly higher total efficacy at 94.87% compared to the control group, which achieved 76.92% efficacy ($P < 0.005$). See **Table 1** for further details.

Table 1. compares the clinical curative effect of different groups of patients [*n* (%)]

Group	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Control group	11 (28.20)	9 (23.08)	10 (25.64)	9 (23.08)	30 (76.9)
Experimental group	21 (53.84)	10 (25.64)	6 (15.39)	2 (5.13)	37 (94.87)
χ^2					5.185
P					< 0.05

3.2. Changes in liver function

Before treatment, there was no difference in the ALT, AST, and ALP levels between both groups of patients ($P > 0.05$). After treatment, the ALT, AST, and ALP levels in the experimental group were significantly lower than those in the control group ($P < 0.005$). See **Table 2** for further details.

Table 2. Comparison of changes in liver function levels in different groups of patients (mean ± standard deviation, U/L)

	ALT		AST		ALP	
Group	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**
Control group	60.65 ± 5.39	42.30 ± 3.62	62.43 ± 5.57	44.55 ± 3.95	135.60 ± 9.77	72.06 ± 6.46
Experimental group	60.33 ± 5.36	34.52 ± 4.55	62.46 ± 5.60	36.41 ± 4.80	135.63 ± 9.81	54.60 ± 5.01
t	0.263	8.356	0.024	8.178	0.014	13.338
P	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05

3.3. Complication rate

The experimental group recorded a significantly lower total complication rate of 10.25% compared to the control group, where the total complication rate stood at 28.21% ($P < 0.005$). Refer to **Table 3** for details.

Table 3. Comparison of total complication rates among patients in each group [*n* (%)]

Group	Fever	Rebleeding	Incision infection	Lung infection	Total
Control group	4 (10.26)	2 (5.13)	3 (7.69)	2 (5.13)	11 (28.21)
Experimental group	2 (5.13)	0 (0.00)	1 (2.56)	1 (2.56)	4 (10.25)
χ^2					4.044
P					< 0.05

4. Discussion

Cirrhotic portal hypertension is relatively difficult to treat, and the disease manifests as splenomegaly, portal vein collateral circulation, etc., accompanied by spontaneous peritonitis, gastrointestinal bleeding, and other symptoms [6,7]. The cause of portal hypertension remains not well-understood, but it is generally associated with increased portal vein resistance ("backward-flow" theory) and increased portal vein blood flow ("forward-flow" theory) [8,9]. The esophageal and gastric varices formed by the opening of portal vein collaterals are the main cause of death due to rupture and bleeding. Studies show that most patients with liver cirrhosis and portal hypertension are accompanied by symptoms of upper gastrointestinal bleeding, and the mortality rate is as high as 58%. The key to the treatment of portal hypertension in liver cirrhosis is to control bleeding and eliminate hypersplenism [10,11].

In this study, the effects of surgical devascularization (control group) and interventional devascularization (experimental group) in the treatment of liver cirrhosis and portal hypertension were compared. Better improvement was seen in the functional indicators of the patients in the experimental compared to the control group, and complication rate of the experimental group was also lower than that of the control group. Therefore, it is clear that interventional devascularization is more effective and safer than surgical devascularization in treating cirrhotic portal hypertension. The treatment methods for cirrhotic portal hypertension include drug therapy, surgery, endoscopic treatment, etc., which are all effective but each comes with certain shortcomings [12,13]. Interventional devascularization is superior over other treatment methods because medication is less effective, and surgical intervention has a higher mortality rate, and liver transplantation a very demanding procedure. Partial splenic embolization can achieve good results by effectively inhibiting hypersplenism and reducing the size of an overly large spleen, so as to improve immune hemocytopenia and correct hypersplenism. Previously, it was believed that the portal vein blood flow will not change after splenectomy or devascularization, and the blood flow may increase [14]. However, some studies showed that the portal vein blood flow decreased significantly after splenectomy or devascularization, which was mainly due to the increase of portal vein blood flow caused by the splenic vein [15]. The selection of the most appropriate portal vein branch for the procedure is crucial. Achieving super-selective intubation for all varicose veins is essential, and employing a slow and intermittent injection of embolic agents helps prevent embolic agent reflux and shunts from entering the vein. The combined use of spring steel ring, gelatin sponge, and absolute ethanol can enhance the embolization effect. Precise positioning by DSA can reduce the occurrence of postoperative complications and reduce the risk of rebleeding. In interventional devascularization, the risk of rebleeding is significantly reduced as it ensures comprehensive coverage of the main portal vein and ectopic collaterals. The procedure involves direct portal vein angiography during which collateral veins are

fully exposed, eliminating the possibility of missing any critical issues.

5. Conclusion

In conclusion, interventional devascularization is effective in treating cirrhotic portal hypertension, which is reflected in the improvement of liver function and high safety, and it is worthy of promotion and application.

Disclosure statement

The authors declare no conflict of interest.

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Oncology Treatment Discovery, 2023, Volume 1, Issue 2
http://ojs.bbwpublisher.com/index.php/OTD

Analysis of the Effect of Bevacizumab as an Anti-VEGFR Pathway Drug in the Clinical Treatment of Lung Cancer

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Abstract: *Objective:* To analyze the effect of treatment with bevacizumab, an anti-vascular-endothelial-growth-factor (anti-VEGFR) pathway drug, in patients with lung cancer. *Methods:* 60 patients with lung cancer that were admitted from October 2021 to February 2023 were used as research subjects, the patients were divided into two groups using the random number table. Group A was treated with bevacizumab + protein bound paclitaxel combined with carboplatin + cisplatin, and Group B was treated with protein-bound paclitaxel combined with carboplatin + cisplatin. The efficacy of both treatments and the tumor marker levels, the immune function, and the toxicity and side effects between the two groups were compared. *Results:* The efficacy of the lung cancer therapy in group A was higher than that in group B, $P < 0.05$; serum tumor markers such as carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125) of the patients of group A were significantly higher than those in group B, $P < 0.05$; $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and other immune indicators of the patients in group A were better than those in group B, $P < 0.05$; the toxicity and side effects of the treatment received in group A was no different than group B, $P > 0.05$. *Conclusion:* Bevacizumab, an anti-VEGFR pathway drug, is effective and feasible in treating lung cancer. Besides, it inhibits the progression of cancer, regulates the body's immune function, thus prolonging the survival of patients.

Keywords: Anti-VEGFR drugs; Bevacizumab; Lung cancer; Efficacy

Online publication: September 26, 2023

1. Introduction

Lung cancer is one of the most common malignant tumors and a leading cause of patient mortality. The most common pathological type is non-small cell lung cancer (NSCLC). Following the onset of lung cancer, tumor cell proliferation is typically slow, and metastasis occurs later in the disease course. Patients often remain asymptomatic during the early stages of the illness, which can lead to a delay in the optimal timing of surgery once the diagnosis is established [1]. Chemotherapy is commonly used in treating patients with advanced lung cancer. The drugs used are protein-bound paclitaxel combined with carboplatin, cisplatin, etc., which can prolong the survival of patients. However, the chances of a 5-year survival of lung cancer patients are still relatively low [2]. In recent years, targeted drugs have been gradually used in the treatment of lung cancer, such

as bevacizumab, which can act on vascular endothelial growth factor (VEGF), block the growth of tumor blood vessels, and induce tumor cell death. It is applicable to the treatment of advanced malignant tumors [3]. In this paper, 60 patients with lung cancer who were treated from October 2022 to February 2023 were used as a sample to explore the treatment effect of bevacizumab.

2. Materials and methods

2.1. Information

60 lung cancer patients from October 2021 to February 2023 were included in this study, and the patients were divided into 2 groups by the random number table method. Group A consisted of 19 males and 11 females, aged 40–72 years, average 52.88 ± 1.89 years; group B, 21 males, 9 females, aged 41–73 years, average 53.01 ± 1.91 years old. There was no difference in the data of patients with lung cancer in group A and group B, $P > 0.05$.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (i) expected survival of more than 3 months, (ii) imaging and pathology results suggest lung cancer, (iii) signed an informed consent, (iv) requires chemotherapy.

Exclusion criteria: (i) patients with mental and intellectual abnormalities, (ii) patients with secondary malignant tumors, (iii) patients allergic to chemotherapy drugs or bevacizumab, (iv) patients with cardiac dysfunction.

2.3. Treatment methods

The chemotherapy regimen of group A is the same as that of group B. As for the patients in group A (manufactured by Hengrui Pharmaceutical Company; approval number: S20100024) 7.5 mg/kg bevacizumab was administered intravenously once a day, and one course of treatment lasted for 4 weeks. A total of 4 courses of treatment were carried out for each patient.

Group B was given protein-bound paclitaxel combined with carboplatin (manufactured by Jiangsu Hansoh Pharmaceutical Group Co., Ltd.; approval number: H20093996) combined with cisplatin (manufactured by Dezhou Deyao Pharmaceutical Co., Ltd.; approval number: H20093996). Protein-bound paclitaxel combined with 500 mg/m^2 carboplatin and 75 mg/m^2 cisplatin were administered once a day, both by intravenous infusion. one course of treatment lasted for 4 weeks. A total of 4 courses of treatment were carried out for each patient. During chemotherapy, it is important to pay attention to the management of allergies and nausea, and the patient should also be well hydrated.

2.4. Observation indicators

Efficacy was assessed as follows: Complete remission (CR) indicated the absence of lung cancer lesions for four consecutive weeks, partial response (PR) meant a reduction of over 30% in the sum of the largest tumor diameters for four consecutive weeks, stable disease (SD) was recorded for ≤ 30% reduction or < 20% increase in the sum of the largest tumor diameters for four consecutive weeks, progressive disease (PD) was noted for a ≥ 20% increase in the sum of the largest tumor diameters for four consecutive weeks. The disease control rate (DCR) was calculated as CR rate + PR rate + SD rate. Tumor markers, including carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and carbohydrate antigen 125 (CA125), were monitored before and after medication, as well as changes in $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ratios. Toxic and side effects such as abnormal liver function, bone marrow suppression, and chemotherapy-induced thrombocytopenia were recorded for both groups.

2.5. Statistical analysis

The data from lung cancer patients were analyzed using SPSS 21.0 software. Count data for lung cancer patients were expressed as percentages and analyzed using the χ^2 test, while mean ± standard deviation was used for measurement data of lung cancer patients and analyzed with a *t*-test. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Efficacy

The efficacy of the treatment received by group A was higher than that in group B, $P < 0.05$. As in **Table 1**.

Table 1. Efficacy of treatment received by group A and group B (*n* [%])

Group	CR	PR	SD	PD	DCR
Group A (*n* = 30)	0 (0.00)	9 (30.00)	18 (60.00)	3 (10.00)	27 (90.00)
Group B (*n* = 30)	0 (0.00)	3 (10.00)	13 (43.33)	14 (46.67)	16 (53.33)
χ^2	-	-	-	-	9.9316
P	-	-	-	-	0.0016

3.2. Tumor markers

Before treatment, there was no difference in the tumor markers between group A and group B, $P > 0.05$. After treatment, the tumor markers such as CEA, NSE, and CA125 in group A were better than those in group B ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of tumor markers (mean ± standard deviation)

Group	CEA (μg/L)		NSE (μg/L)		CA125 (mg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A (*n* = 30)	124.14 ± 2.36	25.41 ± 1.51	17.87 ± 2.43	5.59 ± 1.84	275.36 ± 3.28	27.11 ± 2.36
Group B (*n* = 30)	124.19 ± 2.39	49.31 ± 1.69	17.91 ± 2.39	9.71 ± 1.96	275.41 ± 3.31	45.73 ± 2.87
t	0.0815	57.7614	0.0643	8.3941	0.0588	27.4472
P	0.9353	0.0000	0.9490	0.0000	0.9533	0.0000

3.3. Immune function

Before treatment, there was no difference in the immune function indexes between group A and group B, $P > 0.05$. After treatment, immune indexes such as $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ in group A were better than those in group B, $P < 0.05$, as shown in **Table 3**.

Table 3. Comparison of immune function (mean ± standard deviation)

Group	$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$ (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A (*n* = 30)	27.01 ± 1.87	29.43 ± 2.01	23.21 ± 1.42	19.43 ± 1.32	1.25 ± 0.21	1.39 ± 0.17
Group B (*n* = 30)	27.05 ± 1.91	23.43 ± 1.63	23.24 ± 1.39	22.08 ± 1.36	1.23 ± 0.19	1.08 ± 0.09
t	0.0820	12.6991	0.0827	7.6584	0.3868	8.8272
P	0.9350	0.0000	0.9344	0.0000	0.7003	0.0000

3.4. Toxicity and side effects

The toxicity of both types of treatment were no different ($P > 0.05$), as shown in **Table 4**.

Table 4. Comparison of the toxicity and side effects of both groups (n [%])

Group	Abnormal liver function	Myelosuppression	Thrombocytopenia	Incidence rate
Group A ($n = 30$)	1 (3.33)	1 (3.33)	3 (10.00)	6 (20.00)
Group B ($n = 30$)	2 (6.67)	1 (3.33)	2 (6.67)	5 (16.67)
χ^2	-	-	-	0.1113
P	-	-	-	0.7386

4. Discussion

Lung cancer is a relatively common malignant tumor, and it comes with several symptoms. (i) Coughing: Coughing is the primary symptom of lung cancer. This is because the function of bronchial mucus secretion will be impaired due to tumor cell infiltration. Paroxysmal dry cough is common among lung cancer patients, which cannot be treated with conventional cough medicine. In addition, smoking further aggravates coughing. (ii) Hemoptysis: Tumor tissue possesses an abundant blood supply, and severe coughing can lead to the rupture of blood vessels within it, potentially triggering hemoptysis. This is especially significant in cases where larger blood vessels rupture, resulting in more substantial episodes of hemoptysis. (iii) Chest pain: Most patients with lung cancer experience chest tightness or chest pain, and in severe cases, throbbing pain. (iv) Chest tightness: Central lung cancer patients often experience chest tightness, and if secondary lung failure develops, it can be accompanied by dyspnea. This is often associated with factors such as airway obstruction, atelectasis, pleural effusion, and lymph node metastasis, making treatment challenging. (v) Hoarseness is an uncommon symptom in lung cancer patients and is typically associated with lymph node metastasis and blockage of the recurrent laryngeal nerve. In severe cases, it can lead to airway obstruction and impaired respiratory function [5,6].

There are serval causes of lung cancer. (i) Smoking: The incidence of lung cancer is associated with the duration of smoking. (ii) Occupational exposure: working in special environment for a long time, such as exposure to ammonia, formaldehyde, coal tar and other substances. (iii) Air pollution: vehicle exhaust emissions and industrial waste gas increase the risk of lung cancer. (iv) Ionizing radiation: Long-term high-dose exposure to ionizing radiation can induce lung cancer. (v) Diet: Individuals with a low daily intake of fruits and vegetables often have low levels of β-carotene in their bodies. (vi) History of pulmonary diseases: Those with history of bronchiectasis and pulmonary tuberculosis are more likely to develop lung cancer. Since there are no specific signs in the early stages of lung cancer, when it advances to the middle and late stages, it becomes necessary to combine chemotherapy regimens to stabilize the disease, delay the progression of cancer foci, and enhance the 5-year survival rate of patients [7,8].

At present, protein-bound paclitaxel combined with carboplatin is mostly used in the treatment of lung cancer patients. Taxol protein-bound combined with carboplatin is a targeted cytotoxic drug that acts on multiple targets, disrupting various enzyme activation processes within the human body. It inhibits dihydrofolate reductase and other catalytic reactions, subsequently counteracting the body's synthesis of purine and thymidine nucleotides. This inhibition suppresses tumor cell RNA and DNA replication, leading to a slowdown in tumor proliferation. [9,10]. Cisplatin is administered intravenously and directly acts on tumor cells, allowing water molecules to replace chloride ions in tumor cells, causing water molecules to enter the nucleus of tumor cells. The water molecules are then replaced by guanine, which results in the inhibition of DNA transcription of

tumor cells, leading to apoptosis, thus delaying tumor progression [11,12]. As per relevant literature, the 5-year survival rate for patients treated with protein-bound paclitaxel in combination with carboplatin + cisplatin chemotherapy for lung cancer remains relatively low. This outcome is associated with tumor cell metastasis, which is closely linked to both neovascularization and the infiltration of tumor cells [13]. When the tumor cells in lung cancer patients exceed 2 mm in diameter, independent vasculature is needed to supply energy to the tumor cells. However, new tumor blood vessels in the body need the help of vascular endothelial growth factor (VEGF) and other cytokines. Therefore, VEGF and vascular endothelial growth factor (VEGFR) targeted therapy can be carried out during the treatment of lung cancer patients. Bevacizumab is a novel targeted therapy drug that contains human genes (93.00%) and mouse genes (7.00%). The two gene fragments competitively inhibit each other and have the ability to bind to endogenous VEGFR, resulting in the inactivation of VEGF. This process effectively disrupts the proliferation of endothelial cells and blocks the formation of new blood vessels in the tumor's surrounding area. Furthermore, it can also inhibit the functioning of the tumor cell implantation system. By disrupting the supply of nutrients and oxygen to the tumor tissue, it effectively hinders tumor growth, thus demonstrating anti-tumor properties. Additionally, bevacizumab can increase blood vessel permeability, leading to a higher concentration of locally administered chemotherapeutic drugs and thereby enhancing treatment efficacy [14]. Protein-bound paclitaxel combined carboplatin + platinum chemotherapy, combined with bevacizumab therapy can optimize the prognosis of lung cancer patients.

Combined with the data analysis in this paper, the lung cancer treatment in group A was higher than that in group B ($P < 0.05$); serum tumor markers such as CEA, NSE, and CA125 in group A were lower than those in group B ($P < 0.05$); group A's $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and other immune indicators were better than those in group B ($P < 0.05$); the incidence of toxic and side effects in patients with lung cancer in group A was not different from that in group B, ($P > 0.05$). It is suggested that conventional chemotherapy + bevacizumab treatment can enhance the immune function of patients and delay the progression of cancer. Besides, the addition bevacizumab does not increase the toxicity of the treatment. Bevacizumab belongs to the main monoclonal antibody, which can prevent edema, induce tumor cell apoptosis by blocking VEGF activity, and has the effect of anti-angiogenesis in the adjacent area of the tumor, which is beneficial to the prognosis of lung cancer patients.

5. Conclusion

In summary, bevacizumab, an anti-VEGFR pathway drug, can regulate the immune function of the body and delay the progression of lung cancer for lung cancer patients. Besides the addition of bevacizumab does not increase the toxicity and side effects, which helps prolong the survival of lung cancer patients and has promotion value.

Disclosure statement

The author declares no conflict of interest.

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Oncology Treatment Discovery, 2023, Volume 1, Issue 2
http://ojs.bbwpublisher.com/index.php/OTD

Research Progress on Clinical Treatment of Hemangioma and Vascular Malformation in Children

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Abstract: Childhood hemangioma is a common benign tumor composed of vascular endothelial cells that occurs mostly in children, with a high incidence rate, generally 4–10%. The incidence rate is as high as 75% within a few weeks after birth, especially in the skin and subcutaneous tissue. Hemangioma can be invasive, growing rapidly, and may lead to spontaneous ulceration. It can also regress on its own. When it affects multiple areas on the head and face, it can create a significant mental and psychological burden for both children and parents. Treatment methods for hemangiomas have become more mature, with expert consensus and clinical practice guidelines available. Understanding of how these treatments work has also improved. It is important to review the available treatment options to assist both healthcare providers and parents in choosing the most suitable treatment for children with hemangiomas. This helps in making informed decisions about treatment methods.

Keywords: Children hemangioma; Vascular malformation; Clinical treatment; Progress

Online publication: September 26, 2023

1. Introduction

The implementation of China's two-child policy has resulted in an increased number of newborns. Consequently, there has been a year-on-year increase in cases of hemangiomas in children [1]. Hemangioma is a common benign tumor composed of vascular endothelial cells that mostly occurs in children, with an incidence of 4–10% [2,3]. The incidence rate is as high as 75% within a few weeks after birth. Hemangioma is usually visible in various parts of the human body, especially the skin and subcutaneous tissue. Hemangioma can be invasive, growing rapidly, and may lead to spontaneous ulceration. Multiple hemangiomas can also occur at

different areas of the face. Therefore, it brings great mental and psychological burden to children and parents, especially in the proliferative period. Hemangiomas can potentially lead to damage to muscle or skin blood vessels, secondary infections, and, in severe cases, ulceration. These complications can result in significant issues such as damage to one's appearance and even vision loss [4]. Treatment methods for hemangiomas have become more mature, with expert consensus and clinical practice guidelines available. Understanding of how these treatments work has also improved. It is important to review the available treatment options to assist both healthcare providers and parents in choosing the most suitable treatment for children with hemangiomas. This helps in making informed decisions about treatment methods.

2. Interventional therapy

Interventional therapy entails introducing an embolic agent into the blood supply and return site of the hemangioma through a catheter. This changes the hemodynamics of blood flow within the hemangioma. Subsequently, a sclerosing agent is percutaneously injected under ultrasound guidance. The sterile inflammatory reaction triggered by the hardening foam promotes the occlusion of the hemangioma, ultimately achieving the desired therapeutic outcome [1,5-8]. For different hemangiomas and vascular malformations, a combination of different sclerosing agents such as lauromacrogol or polidocanol injection [9] has been proven effective. Interventional therapy is widely employed in clinical practice for treating pediatric hemangiomas due to its advantages like minimal trauma, notable efficacy, strong repeatability, and its non-interference with subsequent treatments. It is generally well-received by parents, making it the primary approach for pediatric hemangioma treatment in clinical practice.

3. Drug treatment

In clinical practice, commonly used drugs for treating infantile hemangioma include propranolol, bleomycin, pingyangmycin, and others [10]. Propranolol is primarily administered orally, while bleomycin and pingyangmycin are mainly applied externally or subcutaneously [11].

The use of propranolol in the treatment of infantile hemangioma began in 2008 and demonstrated significant efficacy from its initial application [12]. Clinical practice also proved the efficacy of propranolol in the treatment of infantile hemangioma. The main drug in the treatment of hemangioma. As a synthetic non-selective β-adrenergic receptor blocker, it can block β1 and β2 receptors, causing a decrease in heart rate and blood pressure [13]. The mechanism of action of propranolol in the treatment of hemangioma has not been fully understood. It is generally believed that in the early stages, propranolol reduces the release of nitric oxide within 1–3 days after treatment initiation, leading to vasoconstriction. In the middle stage, it inhibits angiogenesis by blocking pro-angiogenic signals and induces apoptosis of endothelial cells, resulting in a long-term therapeutic effect [14]. Propranolol may also induce apoptosis of various types of cells including endothelial cells *in vitro* by blocking β2 receptors [15]. Therefore, induction of apoptosis may be another mechanism of therapeutic effect of propranolol on hemangiomas. Propranolol is effective as a first-line oral treatment of hemangiomas, but it also has side effects. Its main side effects are bronchospasm, hypotension, hypoglycemia, bradycardia, etc [12,13]. After being approved for marketing, it was discovered that propranolol might lead to adverse reactions, including agranulocytosis, hallucinations, purpura, and psoriasis-like dermatitis. Additionally, its efficacy in treating larger hemangiomas is not satisfactory. Therefore, the combination of drugs is mostly used to treat superficial hemangiomas with a small range of involvement.

4. Surgical treatment

Surgical treatment can be considered for deep or mixed hemangiomas that do not respond to medical therapy, pose life-threatening or function-threatening risks (e.g., airway obstruction), or do not improve with local therapy due to contraindications or treatment failure. This option is particularly relevant when the hemangioma is located on the scalp or trunk, and when it is situated in a concealed or deep area, possibly in conjunction with vascular malformation [2,16]. Surgical intervention is more effective than medications, but it comes with certain risks and complications [17]. For example, it may cause postoperative incision scars, skin color and skin texture inconsistencies in the affected area, etc., which may impact the child's mental health or future opportunities. This ensures that parents have a complete understanding and can carefully weigh the pros and cons of surgery. Typically, surgical intervention is not the primary treatment option for hemangiomas due to the potential for varying degrees of scarring.

5. Laser treatment

Multiple laser options are available for hemangioma treatment, including dot matrix CO_2 laser, pulsed dye laser, frequency-doubled Nd-doped yttrium aluminum garnet (Nd:YAG) laser, and photodynamic therapy, among others [17,18]. Different laser therapy devices have different working principle, therapeutic effects, and functions. For example, when frequency-doubling Nd-doped YAG laser irradiates hemangioma lesions, melanin particles in the epidermis can be competitively absorbed due to poor laser penetration [19]. Pulsed dye laser is designed according to the "selective photothermal effect theory," which has better curative effect and fewer side effects, but there are still adverse reactions such as purpura, skin texture changes, temporary pigment changes, and atrophic scars after use. The advantages of photodynamic therapy are high tissue selectivity, definite curative effect, and small systemic adverse reactions. However, due to the use of photosensitizers, postoperative light protection is required [21]. Due to its strong penetrating power, photodynamic therapy is currently mostly used for the elimination of postoperative scars.

6. Other treatments

In addition to the above-mentioned treatment methods for hemangiomas that are widely used at present, there are other methods such as hormone therapy, interferon therapy, cryotherapy, and radionuclide therapy for hemangiomas. However, it is not easy to control the dosage of drugs, hormones, and interferon used. These drugs might have a greater impact on the body in the later stages of life. Besides, the radiation produced in these therapies might cause hypopigmentation spots, bone growth inhibition, and scars at the treatment site. These methods are rarely used clinically at present [16,17,21].

For all infantile hemangioma patients, the selection of treatment measures should depend on the following three aspects, in order of importance: the location of the tumor, the age of the child at the time of treatment, and the size of the tumor [22]. The above treatment methods have their own indications and side effects in different degrees. In order to achieve a better therapeutic effect in the clinical treatment of hemangioma, a combination of multiple treatment methods is often used. The main goal of treating hemangiomas is not to eliminate all lesions but to alleviate the symptoms and control the progression of disease [9]. Therefore, it is very important to find a balance in the treatment, which includes aspects like safety, bodily functions, and especially aesthetics or appearance. It is important not to bring extra burden to the patients and their families due to excessive treatment.

Disclosure statement

The authors declare no conflict of interest.

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Oncology Treatment Discovery, 2023, Volume 1, Issue 2
http://ojs.bbwpublisher.com/index.php/OTD

Efficacy of GnRH-α Combined with Mirena in the Treatment of Adenomyosis and its Impact on Ovarian Function

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Abstract: *Objective:* To discuss and analyze the clinical effects and changes of ovarian function after GnRH-α combined with Mirena treatment in patients with adenomyosis. *Methods:* The research subjects in this study were all adenomyosis patients (60 cases) who were admitted to our hospital from January 2020 to June 2022. They were randomly divided into a control group (30 cases, received Mirena treatment) and an observation group (30 cases, received GnRH-α combined with Mirena treatment). The relevant indicators of both groups were compared. *Results:* After treatment, both the observation group and the control group exhibited reduced uterine volume, thinner endometrial thickness, lower VAS score, PBAC score, serum FSH, LH, and E2 levels compared to pre-treatment values. The serum AMH level and various FSFI scores were higher than before treatment, with the observation group showing a more noticeable increase. Additionally, the observation group had a lower incidence of adverse reactions compared to the control group (all $P < 0.05$). *Conclusion:* The application of GnRH-α combined with Mirena in patients with adenomyosis can reduce the amount of menstrual bleeding, reduce the volume of the uterus, relieve pain, promote the recovery of ovarian function, improve the quality of sexual life, and it is safe. Therefore, this method of treatment should be promoted in clinical practice.

Key words: Adenomyosis; Mirena; Gonadotropin-releasing hormone agonist drugs; Ovarian function

Online publication: September 26, 2023

1. Introduction

Adenomyosis is a relatively common gynecological disease. After the onset of the disease, patients often present with abnormally increased menstrual flow and dysmenorrhea. The continuous development can affect their ovarian function, and even cause infertility [1]. Common treatment methods for this disease include surgery and conservative treatment. Surgical treatment is highly effective, but it cannot preserve the physiological function of the uterus, and some patients may develop resistance. The Mirena IUD is a topical hormonal contraceptive method that can significantly reduce menstrual bleeding and provide long-term effectiveness. However, there is a risk of hair loss, which could potentially affect its effectiveness [2]. Therefore, there is still a need to develop more comprehensive and effective treatment methods for this disease. Gonadotropin-releasing hormone agonist drugs (GnRH-α) are currently widely used in clinical practice, which can regulate the ovarian function of

patients and improve the therapeutic effect [3]. In this study, we analyzed the clinical outcomes and changes in ovarian function in patients with adenomyosis who underwent treatment with GnRH-α in combination with Mirena.

2. Materials and methods

2.1. Basic information

The research included 60 adenomyosis patients who were admitted to our hospital between January 2020 and June 2022. These patients were randomly divided into two groups: the control group (30 cases) and the observation group (30 cases).

In the control group, the duration of the disease ranged from 1 to 6 years, with an average of 3.11 ± 0.24 years. The number of pregnancies varied from 1 to 4, with an average of 2.14 ± 0.23. The patients' ages ranged from 25 to 65 years old, with an average age of 47.89 ± 3.75 years. In the observation group, the duration of the disease ranged from 1 to 5 years, with an average of 3.09 ± 0.23 years. The number of pregnancies varied from 1 to 5, with an average of 2.16 ± 0.25. The ages of patients ranged from 26 to 65 years, with an average of 47.87 ± 3.73 years. The patients were diagnosed according to *Practical Obstetrics and Gynecology (2nd Edition)* [4]. Inclusion criteria: those who were married but were not planning to have children in the future, those with abnormal menstrual flow, those with functioning ovaries, etc. Exclusion criteria: those who received other treatments before enrollment, those who were intolerant to treatment-related drugs, those with blood diseases, etc. This study was reviewed and approved by the Medical Ethics Committee of our hospital. All research subjects voluntarily signed relevant consent forms after understanding the research content and the risks involved.

2.2. Methods

The menstrual status of the patient was observed, and levonorgestrel intrauterine system treatment was given 3 days after the menstruation period. The treatment was performed in an aseptic environment. A slider was inserted and pushed until it reached the top of the uterus, and the depth of the uterine cavity was measured after the intrauterine system was completely placed in the tube. The slider was placed at a distance of 1.8 cm from the cervix. After 5 to 10 seconds, the slider was slowly to the bottom of the uterus. The tail extended 2 cm from the cervix, the slider was kept in the body for 6 months. The observation group received a subcutaneous injection of leuprolide acetate microspheres (3.75 mg) (Shanghai Livzon Pharmaceutical Co., Ltd., National Pharmaceutical Approval: H20093852) on the 1st day of menstruation every 4 weeks. After 3 consecutive injections, Mirena rings were placed in accordance with the control group's protocol.

2.3. Observation indicators

(i) A color Doppler ultrasonic diagnostic system (Guangdong Jizhun 20172231168, model: P70T) was used to measure the uterine volume and endometrial thickness. The degree of pain was scored with reference to the Visual Analogue Scale (VAS), which ranged from 0–10 points [5], the higher the score, the higher the degree of pain. The menstrual fluid volume was evaluated based on the Blood Volume Graphic Analysis Score (PBAC) [6], and > 80 points indicated excessive menstrual flow. (ii) About 3 mL of venous blood was collected from the patients before and after treatment. After drawing the patient's blood, the serum centrifuged at a speed 2800 r/min for 10 min, and the levels of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2) and anti-Müllerian hormone (AMH) of the patients were detected through the enzyme-linked immunosorbent assay. (iii) The quality of sexual life of the patients was evaluated by the Female Sexual Function Index (FSFI) [7], with each item ranging from 0–6 points (sexual desire, orgasm, sexual excitement,

vaginal lubrication, etc.), and the worse the quality of sexual life, the lower the score. (iii) The occurrence of adverse reactions such as abdominal pain, irregular bleeding, and skin rash during treatment were recorded.

2.4. Statistical methods

A *t*-test was used to compare the measurement data of both groups and is expressed in the form of mean ± standard deviation. A χ^2 test was used to compare the count data and is expressed in the form of *n* (%). All data were analyzed using SPSS 20.0, and $P < 0.05$ indicates statistical significance.

3. Results

3.1. Uterine volume, endometrial thickness, VAS score, PBAC score

The uterine volume, endometrial thickness, VAS score, and PBAC score of the two groups are shown in **Table 1**. The results demonstrated that following treatment, the uterine volume and endometrial thickness decreased, and the VAS and PBAC scores were lower compared to before treatment in both groups. However, these changes were more prominent in the observation group, and the differences in the data were statistically significant ($P < 0.05$) when compared to the control group.

Table 1. Comparison of uterine volume, endometrial thickness, VAS score, and PBAC score between the two groups before and after treatment (mean ± standard deviation)

Group	Number of cases	Uterine volume (m^2)		Endometrial thickness (mm)		VAS score (points)		PBAC score (points)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	30	156.75 ± 8.15	105.71 ± 6.29*	9.14 ± 1.01	6.84 ± 0.27*	7.46 ± 1.04	2.77 ± 0.64*	144.11 ± 9.25	66.97 ± 5.51*
Observation group	30	156.73 ± 8.17	82.92 ± 4.20*	9.12 ± 1.02	5.16 ± 0.12*	7.44 ± 1.02	1.05 ± 0.22*	144.13 ± 9.23	56.01 ± 5.27*
t		0.009	16.504	0.076	31.143	0.075	13.921	0.008	7.873
P		> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05

Note: *$P < 0.05$ compared to before treatment

3.2. Sex hormone levels

Table 2 shows the results related to the levels of sex hormones in the two groups. The findings indicate that after treatment, the serum levels of FSH, LH, and E2 in both groups decreased, while the serum AMH levels increased compared to pre-treatment levels. The changes in the hormone levels of patients in the observation group were more pronounced compared to the control group, with statistically significance ($P < 0.05$).

Table 2. Comparison of sex hormone levels before and after treatment in the two groups (mean ± standard deviation)

Group	Number of cases	FSH (IU/L)		LH (IU/L)		E_2 (pmol/L)		AMH (ng/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	30	74.81 ± 6.66	42.73 ± 4.49*	42.51 ± 8.44	31.13 ± 6.41*	66.11 ± 3.12	48.51 ± 6.11*	3.11 ± 0.25	4.47 ± 0.31*
Observation group	30	74.82 ± 6.68	40.20 ± 3.35*	42.50 ± 8.42	18.15 ± 4.20*	66. 09 ± 3.14	40.03 ± 4.04*	3.13 ± 0.23	4.01 ± 0.24*
t		0.006	2.474	0.005	9.277	0.025	6.341	0.322	6.427
P		> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05

Note: *$P < 0.05$ compared to before treatment

3.3. Quality of sexual life

Table 3 shows the results of the parameters related to the quality of sexual life of both groups. The results showed that the FSFI scores of the observation group and the control group after treatment were higher than those before treatment, with observation group having higher scores than the control group. The differences between the data of both groups after treatment were significant ($P < 0.05$).

Table 3. Comparison of FSFI scores between the two groups before and after treatment (mean ± standard deviation, points)

Group	Number of cases	Sexual desire		Orgasm		Sexual excitement		Vaginal lubrication	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	30	1.31 ± 0.61	2.43 ± 0.33*	1.85 ± 0.34	3.14 ± 0.41*	1.47 ± 0.13	2.53 ± 0.61*	1.27 ± 0.16	3.40 ± 0.51*
Observation group	30	1.30 ± 0.63	4.37 ± 0.47*	1.83 ± 0.32	4.37 ± 0.62*	1.49 ± 0.15	4.38 ± 1.02*	1.25 ± 0.18	5.02 ± 0.46*
t		0.602	18.503	0.235	9.064	0.552	8.526	0.455	12.919
P		> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05

Note: *$P < 0.05$ compared to before treatment

3.4. Adverse reactions

Table 4 shows the results related to the occurrence of adverse reactions in both groups. The total incidence of adverse reactions in the observation group was lower than that that of the control group, and the difference was significant ($P < 0.05$).

Table 4. Comparison of adverse reactions between the two groups during treatment (*n* [%])

Group	Number of cases, *n*	Stomachache	Irregular bleeding	Rashes	Total incidence
Control group	30	2 (6.67)	4 (13.33)	3 (10.00)	9 (30.00)
Observation group	30	1 (3.33)	0 (0.00)	1 (3.33)	2 (6.67)
χ^2					5.455
P					<0.05

Note: *$P < 0.05$ compared to before treatment

4. Discussion

Adenomyosis affects patients' daily life, ovarian function and quality of sexual life to varying degrees. At present, the Mirena birth control ring is a commonly used contraceptive method. It has a significant curative effect, but there is a certain risk of dislocation and hair loss, and the effect of a single application is relatively limited. Therefore, relevant treatment plans should be formulated depending on the patient's condition [8].

Leuprolide is a kind of GnRH-α commonly used in clinical practice. Although it has a high affinity for gonadotropin-releasing hormone receptors, it can significantly promote the body's gonadal hormones, promote the atrophy and apoptosis of endometriotic lesions in patients in a short period of time. Besides, it reduces the amount of bleeding while reducing the volume of the uterus and plays an auxiliary role in the fixation of IUDs, which in turn reduces the rate of disengagement and cause less pain [9]. The results of this study revealed that the observation group exhibited a larger decrease in uterine volume and thinner endometrial thickness compared to the control group after treatment. Additionally, the VAS and PBAC scores in the observation group were lower

than those in the control group. These findings suggest that the combined treatment of GnRH-α and Mirena in adenomyosis patients can effectively decrease menstrual bleeding, reduce uterine volume, and alleviate pain. These outcomes are consistent with the research conducted by Zhu *et al* [10].

FSH, LH, E_2, and AMH are all important indicators reflecting the body's sex hormone levels, and they are also the main indicators of the ovarian function [11]. Patients with adenomyosis may experience varying degrees of ovarian function decline. Besides, the level of sex hormones may become disordered, which may affect quality of the patient's sexual life. Leuprolide can significantly inhibit the progesterone in the myometrium, reduce the sensitivity of peptidase decomposition, and shorten the release time of pituitary luteinizing hormone while inhibiting the secretion of sex hormones in the body, thereby regulating ovarian function, which is conducive to improving the clinical symptoms of patients and improving the quality of their sexual life [12]. In addition, GnRH-α combined with Mirena treatment can increase the local drug concentration while regulating the body's sex hormones, which can effectively reduce the risk of irregular bleeding and abdominal pain [13,14]. The results of this study showed that after treatment, the serum FSH, LH, and E2 levels in the observation group were lower than those of the control group, whereas the serum AMH levels and FSFI scores were higher than those of the control group.

5. Conclusion

In summary, the application of GnRH-α combined with Mirena in patients with adenomyosis can reduce menstrual bleeding, reduce uterine volume, relieve pain, promote the recovery of ovarian function, improve the quality of sexual life, and it is safe. Therefore, this method of treatment should be popularized in clinical practice.

Disclosure statement

The author declares no conflict of interest,

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Oncology Treatment Discovery, 2023, Volume 1, Issue 2
http://ojs.bbwpublisher.com/index.php/OTD

Advances in Neoadjuvant Immunotherapy for Locally Advanced Esophageal Cancer

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Abstract: Esophageal cancer is one of the common malignant tumors in China with a high mortality rate. Neoadjuvant chemoradiotherapy (nRCT) is currently the primary treatment method for locally advanced esophageal cancer. However, nRCT has not been not widely applied in China due to several reasons. First, the radiotherapy equipment and technology vary in different regions, and the learning curve for these technologies is steep, making rapid implementation difficult. Furthermore, the combined toxicity of radiotherapy and chemotherapy can counteract the survival benefits of preoperative treatment. In recent years, a promising approach involves combining neoadjuvant chemotherapy with immunotherapy for patients with locally advanced esophageal cancer. This article offers an overview of the progress in neoadjuvant therapy for this condition.

Keywords: Locally advanced esophageal cancer; Neoadjuvant chemoradiotherapy; Immunotherapy; Neoadjuvant chemotherapy

Online publication: September 26, 2023

1. Introduction

Esophageal cancer is one of the most common digestive tract malignancies in the world. Data from collaborative research by various cancer research centers indicates that, in 2020, there were 604,000 new cases of esophageal cancer globally, which resulted in 544,000 deaths. More men than women were diagnosed with esophageal cancer (age-standardized incidence rate 9.3 vs 3.6/100,000) [1]. There are also differences in the distribution of global incidence rates. In China, the incidence rate of esophageal cancer accounts for 53.7%, with a mortality rate of 55.3%. The main histological type of esophageal cancer in our country is squamous cell carcinoma [2]. Squamous cell carcinoma is strongly associated with lifestyle and dietary habits, such as the consumption of hot foods, hot tea, alcohol, and smoking. Additionally, factors like food spoilage, charcoal, and certain cooking methods like roasting or smoking, as well as water quality, soil composition, and environmental microbial flora, contribute to its development. [3].

The choice of treatment for esophageal cancer mainly depends on the type of case and the stage of the disease. Early esophageal cancer often lacks noticeable clinical symptoms, making it challenging to detect.

As a result, most esophageal cancer patients are diagnosed when the disease has already reached an advanced stage or has metastasized to distant sites. Locally advanced esophageal cancer (locally advanced esophageal carcinoma) refers to esophageal tumors that have locally invaded the adventitia of the esophagus (T3) or adjacent organs (T4), or have local lymph node metastasis (N+) without distant metastasis. The results of Worldwide Esophageal Cancer Collaboration in 2021 show that most of the patients with esophageal cancer are locally advanced esophageal cancer.

Surgical resection is considered the most effective approach for achieving local control in esophageal squamous cell carcinoma. However, for patients with stage IIA to III disease, undergoing surgery alone yields a 5-year survival rate ranging from 20.64% to 34.00%. Unfortunately, many of these patients experience metastasis or local recurrence shortly after surgery, leading to unsatisfactory treatment outcomes [4]. The 3-year and 5-year survival of esophageal cancer patients has increased to 61.6% and 52.9% in primary specialist hospitals. However, the postoperative recurrence rate of locally advanced esophageal cancer is still as high as 33.7% [5]. In recent years, the emergence and advancement of molecular targeted therapy and novel immunotherapy drugs have significantly enhanced the role of systemic drug therapy in managing esophageal cancer and controlling its spread.

2. Literature review

Neoadjuvant chemoradiotherapy (nRCT) is the standard treatment for locally advanced esophageal cancer. The CROSS study established the therapeutic status of NCRT in locally advanced esophageal cancer. A total of 366 patients with locally advanced esophageal cancer were included in the study, and a total of 161 cases received carboplatin + paclitaxel along with radiotherapy (41.4 Gy) before surgery, while the control group underwent surgery alone. The results showed a significant difference in the R0 resection rate (92.00% in the nRCT group vs. 69.00% in the control group, $P < 0.001$). Additionally, the postoperative lymph node positivity rate in the nRCT group was notably lower at 31.00% compared to the control group. Patients who received nCRT had a median OS (overall survival) of 49.4 months compared to surgery alone, compared with 24 months in the control group (HR = 0.657; 95% CI = 0.495–0.871, $P = 0.003$). The absolute benefit in overall survival at 10-year follow-up in 2021 was 13% (38% vs 25%). However, the nCRT group did not lead to a higher incidence of postoperative complications and early mortality, only a few high-grade toxic and side effects, and the difference was not statistically significant ($P > 0.05$). Among the patients in the nRCT group, 47 cases (29%) achieved pathological complete response (pCR). In a subgroup analysis, it was observed that the pCR rates for adenocarcinoma and squamous cell carcinoma were 23.00% and 49.00%, respectively ($P = 0.008$). This suggests that patients with squamous cell carcinoma had better pCR rates compared to those with adenocarcinoma [6].

NEOCRTEC 5010 study [7] included 451 patients with esophageal squamous cell carcinoma with locally advanced esophageal cancer could be surgically resected. Among them, 224 cases in the NCRT group received cisplatin combined with vinorelbine regimen, concurrent radiotherapy (40 Gy/20 times) followed by surgery, and the control group received surgery alone. The R0 resection rate in the nRCT group was 98.40% vs. 91.20% ($P = 0.002$), with a pCR rate of 43.20%. In the updated 2021 results, compared to the operation-only group, patients in the nRCT group showed significantly improved overall survival (HR = 0.74; 95% CI = 0.57–0.97; $P = 0.03$) and disease-free survival time (DFS) (HR = 0.60; 95% CI = 0.45–0.80; $P < 0.001$). The 5-year survival rates were 59.9% (95% CI = 52.9%–66.1%) and 49.1% (95% CI: 42.3%–55.6%) for the two groups, respectively.

3. Current status of treatment for locally advanced esophageal cancer in China

Although nRCT is the standard treatment for locally advanced esophageal cancer, a comprehensive analysis of surgical treatment for esophageal cancer in our country indicates that the utilization rate of nRCT remains low. In the many countries, most patients receive neoadjuvant therapy. The most commonly used with neoadjuvant chemotherapy (nCT) program at home and abroad is platinum combined with fluorouracil or paclitaxel. It is mainly based on clinical research results such as OEO2 and JCOG9907. Researchers believe that administering chemotherapy before surgery can enhance patients' tolerance to treatment, lead to tumor shrinkage, increase the rate of complete tumor removal (R0 resection), eliminate micrometastases, and extend survival. Numerous studies have demonstrated improvements in the short-term response rate and rate of achieving pCR with nCT (35.7%:3.8% [8]; 38.9%:5.6% [9]; 27.6%:4.8% [10]) are lower than nRCT, but whether there is a difference in the overall survival is still debated. Moreover, there are certain difficulties in promoting preoperative radiotherapy and chemotherapy.

The complexity of preoperative radiotherapy and chemotherapy arises from the demands it places on the diagnostic and treatment capabilities of the medical center. It requires a high level of expertise in pre-treatment evaluation, radiotherapy, surgery, nutrition, perioperative care, and pathology. Such a comprehensive approach necessitates close collaboration among various departments, functioning as a multidisciplinary platform. The extensive learning curve involved makes it challenging to rapidly implement these procedures in a short timeframe. Secondly, the combined toxicity of radiotherapy and chemotherapy should be taken in to account. Excessive toxicity not only raises the risk of acute adverse reactions during radiotherapy and chemotherapy but also diminishes a patient's tolerance and necessitates lower dosages of these treatments, potentially affecting their compliance. Furthermore, heightened toxicity can lead to increased perioperative complications and, in severe cases, higher perioperative mortality rates. These adverse outcomes may counteract the survival benefits offered by preoperative chemoradiotherapy.

4. Neoadjuvant immunotherapy

4.1. Immune checkpoint inhibitors

Tumor cells are in a highly immunosuppressive microenvironment, in which programmed death protein 1 (PD-1) and programmed death protein ligand 1 (PD-L1) are important immune checkpoint molecules involved in tumor immune escape. PD-1 is a co-inhibitory receptor induced and expressed on the surface of T cells, B cells, monocytes, and NK cells. It is involved in antigen recognition and is one of the signs of immune cell activation. There are two ligands for PD-1, PD-L1 and PD-L2. PD-L1 is widely expressed on the surface of various cells, including tumor cells, and is the main ligand of PD-1. After PD-1/PD-L1 is combined, it induces the generation of regulatory T cells and maintains their function by down-regulating the activity of the PI3K/Akt pathway, thereby playing an immunosuppressive role. PD-L2 is only expressed on antigen-presenting cells and Th2 cells, and can inhibit the activation of T cells after binding to PD-1. By highly expressing immune checkpoint molecules, tumor cells inhibit the proliferation and activation of T cells, evade the monitoring and elimination of the immune system, and cause immune escape of tumor cells. Therefore, blocking the activation of PD-L1-related pathways can suppress tumors, and this procedure is known as immune checkpoint blockade therapy. By detecting 428 surgically resected esophageal squamous cell carcinoma tissues, it was found that the positive rate of PD-L1 was 79.7%, and the positive rate was closely related to the postoperative disease-free survival and overall survival of patients. Another group of experiments found that PD-L1 was highly expressed in 101 cases of esophageal cancer that did not undergo preoperative chemotherapy or radiotherapy This elevated expression

was linked to unfavorable prognosis, implying that PD-L1 plays a significant role in esophageal cancer progression. Therefore, inhibiting PD-L1's activity could potentially be employed as a treatment approach for esophageal cancer.

4.2. Neoadjuvant concurrent chemoradiotherapy combined with immunotherapy for esophageal cancer

In 2019, the Netherlands conducted the PERFECT study, a phase II single-arm single-center clinical trial [11]. This study recruited 33 patients diagnosed with esophageal adenocarcinoma. The treatment regimen included atezolizumab (1200 mg/kg q3w) in combination with the standard CROSS regimen: paclitaxel (50 mg/m^2 qw) + carboplatin (AUC 2 qw), along with concurrent radiotherapy at a dose of PTV 41.4 Gy/23 f. The study yielded several key findings: a pCR rate of 30% (10 out of 33 patients), a 100% R0 resection rate (all 33 patients achieved complete resection), and zero mortality rates at both the 30-day and 90-day perioperative periods. Common adverse reactions observed in the study included fatigue (95%), mucositis (60%), nausea (53%), and anorexia (43%). Notably, the pCR rate of 30% in this trial represents a significant improvement compared to the standard CROSS regimen. It is important to note that the trial is ongoing, and more comprehensive results are anticipated in the future.

A study by Kelly *et al.* enrolled 10 patients with esophageal adenocarcinoma [12]. The dose of concurrent radiotherapy was PTV 41.4 Gy/23 f. The chemotherapy regimen was paclitaxel (50 mg/m^2 qw) + carboplatin (AUC 2 qw) combined with sodium Vulumab 240 mg or 1 mg/kg q2w ± LAG-3 targeted drug (relatimab 80 mg q2w). The results of the study showed that the overall pCR rate was 40% (4/10); the main adverse reactions were dermatitis (6.3%) and hepatitis (6.3%).

Lee *et al.* from South Korea carried out a phase II single-arm single-center clinical study [13]. In this study, 26 patients with esophageal squamous cell carcinoma were enrolled, and they were treated with paclitaxel (45 mg/m^2 qw) + carboplatin (AUC 2 qw) combined immunotherapy. Pembrolizumab was administered at a dose of 2 mg/kg every 3 weeks, along with concurrent radiotherapy with a dose of PTV 44.1 Gy delivered in 21 fractions. This neoadjuvant therapy was initiated 6 to 8 weeks after surgery. Postoperatively, pembrolizumab at the same dose and schedule was used as adjuvant therapy for up to 2 years, with potential adjustments based on disease progression. The results indicated a promising pCR rate for the primary tumor, which was 46.1% (95% CI = 28.8%–64.6%). However, there was a postoperative mortality rate of 7.7% (2 out of 26 patients), primarily due to acute lung injury. Common adverse reactions included neutrophil cytopenia (50.0%), and liver damage (30.8%). The overall survival rates at 6, 12, and 18 months were 89.3%, 80.8%, and 73.1%, respectively. These findings suggest the potential efficacy of this treatment approach in esophageal cancer patients. Based on the PALACE1 study in China in 2020 [14], 18 patients with esophageal squamous cell carcinoma received a radiotherapy dose of PTV 41.4 Gy/23 f; the concurrent chemotherapy regimen was paclitaxel (50 mg/m^2 qw) combined with carboplatin (AUC 2 qw), and immunotherapy with pembrolizumab (2 mg/kg q3w) was given. Surgery was performed 4 to 6 weeks after the end of neoadjuvant therapy. The overall pCR rate was 56% (10/18), and post-surgery pathology revealed that the major pathologic response MPR rate of the primary tumor was 89% (16/18), while the R0 resection rate was 94% (17/18). The incidence of adverse reactions above grade 3 was 65%. These studies indicate an increased pCR rate with concurrent chemoradiotherapy and immunotherapy, although the difference varies. The combination therapy led to a higher incidence of adverse reactions, but these were generally manageable. Future research should focus on long-term survival outcomes and the development of phase III clinical trials.

4.3. Neoadjuvant chemotherapy combined with immunotherapy for esophageal cancer

Concurrent chemoradiotherapy is relatively unpopular in China. Researchers have been exploring new perioperative treatment methods for esophageal cancer. There has been some research output in the past 3 years. For example, the CheckMate 577 study confirmed that postoperative adjuvant nivolumab can significantly prolong the DFS of patients with locally advanced esophageal cancer and esophagogastric junction cancer after neoadjuvant chemoradiotherapy [15]. The famous KEYNOTE-590 study proved the first-line treatment of pembrolizumab combined with chemotherapy (PF regimen) significantly extends the Combined Positive Score CPS of PD-L1, to ≥ 10 in patients with advanced esophageal squamous cell carcinoma [16], so our country's National Medical Products Administration (NMPA) approved pembrolizumab combined with platinum and fluorouracil chemotherapy drugs in September 2021 as the first-line treatment of locally advanced unresectable or metastatic esophagus or gastroesophageal junction cancer. These studies all suggest the important role of immunotherapy in esophageal cancer.

4.3.1. Nivolumab combined with chemotherapy

The FRONTiER study is a multi-center study conducted by Japanese scholars [17] that involved patients with esophageal squamous cell carcinoma were enrolled, The treatment regimens included fluorouracil (800 mg/m2 on days 1-5 every 3 weeks) + cisplatin (80 mg/m^2 every 3 weeks) in combination with sodium Vulumab (360 mg every 3 weeks for group A; 240 mg every 3 weeks for group B); and docetaxel (70 mg/m^2 every 3 weeks) + fluorouracil (750 mg/m^2 on days 1–5 every 3 weeks) + cisplatin (80 mg/m^2 every 3 weeks) + nivolumab (group C: 360 mg every 3 weeks; group D: 240 mg every 3 weeks). The reported results indicated a pCR rate of 33.3% (2/6) in group A and a 92.3% R0 resection rate, with no dose-limiting adverse reactions observed.

4.3.2. Toripalimab combined with chemotherapy

The phase II study carried out by Li *et al.* [18] used toripalimab 240 mg q3w combined with chemotherapy: nab-paclitaxel (260 mg/m^2 q3w) + carboplatin (AUC 5 q3w), and surgery was performed after 4 weeks of treatment. The overall pCR rate was 16.7% (2/12) and the MPR rate of the primary tumor was 58.3% (7/12) after re-administration of the same drug; the incidence of serious adverse reactions was 11.8%.

4.3.3. Sintilimab combined with chemotherapy

The KEEP-G 03 study came from a Phase Ib/II single-arm multicenter study in China [19], using paclitaxel liposome (135 mg/m2 q3w) + cisplatin (75 mg/m2 q3w) + tegafur (40 mg bid d1-d14 q3w) three-drug combination immunotherapy sintilimab (200 mg q3w), the overall pCR rate was 26.7% (4/15), and the primary tumor MPR rate was 53.3% (8/15). 15); R0 resection rate was 100% 15/15); adverse reactions above grade 3 included lymphopenia (29.4%) and neutropenia (11.8%).

4.3.4. Camrelizumab combined with chemotherapy

The NICE study conducted in China [20] utilized camrelizumab (200 mg every 3 weeks) in combination with chemotherapy: nab-paclitaxel (100 mg/m2 every week) + carboplatin (AUC 5 every 3 weeks), followed by surgery 4 weeks after treatment. In the 2020 ESMO conference report, it was revealed that the overall pCR rate was 45% (5/11), with a primary tumor pCR rate of 54.5% (6/11) and a 100% R0 resection rate (11/11). Grade 3 or higher adverse reactions included neutropenia (72.7%) and thrombocytopenia (18.2%). According to the 2021 ASCO meeting report, with an increased number of participants, updated data indicated that out of 60 patients who underwent surgery, 20 of them (42.5%) achieved pCR. Subsequent Phase II and Phase III studies will be conducted to further validate the survival improvement.

Another study [21] in 2021 used camrelizumab (200 mg q3w) combined with docetaxel (75 mg/m2 q3w) + nedaplatin (75 mg/m^2 q3w). Surgery was performed 4 to 6 weeks after treatment. The results reported at the ASCO GI meeting showed that the R0 resection rate was 100%, 22 of the 33 patients underwent surgery, the overall pCR rate was 31.8% (7/22), 15 cases reached the primary goal, and the MPR rate was 68.2 Notably, there were no immune-related adverse reactions above grade 3, and serious adverse reactions were limited to anemia (3%), with no perioperative deaths reported. These findings suggest that combining immunotherapy with chemotherapy yields favorable results, including effective downstaging, a high MPR rate, and overall efficacy and safety. While some studies have shown pCR rates close to those seen in classic CROSS studies, the long-term survival outcomes after surgery still require further accumulation and validation.

5. Conclusion

Esophageal cancer is a life-threatening disease, and it has burden China greatly. Most patients with esophageal cancer are at the locally advanced stage when they are diagnosed. Therefore, it is important to reduce the perioperative period of patients with locally advanced esophageal cancer so that the patients are able to undergo surgery. Immunotherapy has been the primary option in esophageal cancer treatment, and has been recommended as a guideline for second-line and first-line treatment of advanced esophageal cancer. At present, the research data of neoadjuvant immunotherapy conducted at home and abroad have shown good curative effect, and it also brings us more thoughts. The first is the selection of the treatment population. Not all patients can benefit from immunotherapy, and there are cases of progression and relapse. The current predictive indicators for immunotherapy include PD-L1, TMB, mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H), among which dMMR/MSI-H is more sensitive, and other indicators or new markers need to continue to be explored. A review of several important immunotherapy studies for advanced esophageal cancer, including KN590, CheckMate649, KEYNOTE-181, ATTRACTION-3, and ESCORT, showed that patients with high expression levels of PD-L1 assessed by CPS may benefit from immunotherapy. Additionally, the timing of combining immunotherapy with chemotherapy is a critical consideration, whether it's synchronous or sequential. Theoretically, pretreatment with chemotherapy drugs to induce an inflammatory tumor environment may benefit immunotherapy. An ongoing study is investigating the effect of the sequence of chemotherapy and toripalimab treatment on the rate and safety of pCR in patients with locally advanced esophageal cancer. As of now, the primary endpoint has not been reached, and a phase III study is underway (NCT04280822). Other aspects that require exploration include the time interval between neoadjuvant therapy and surgery, the initiation of postoperative adjuvant therapy, the impact of neoadjuvant therapy on surgical and postoperative complications, how to evaluate patients with complete clinical response (cCR), and whether a watch-and-wait approach without surgery is a viable option. These areas require further investigation.

Disclosure statement

The authors declare no conflict of interest.

Funding

This work was supported by the 2021 Beijing Chaoyang District Science and Technology Plan Project (Project number: CYSF2112).

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Oncology Treatment Discovery, 2023, Volume 1, Issue 2
http://ojs.bbwpublisher.com/index.php/OTD

Effect of "Trinity" Service in Tuberculosis Prevention and Control

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Abstract: *Objective*: To analyze the role of "trinity" service in the prevention and control of tuberculosis. *Methods*: From January 2020 to June 2021, routine tuberculosis prevention and control was carried out, and 40 newly diagnosed tuberculosis patients were included in the routine group. From July 2021 to December 2022, the "trinity" mode of prevention and control was carried out, and 40 newly diagnosed tuberculosis patients were included in the research group. The differences in referral follow-up, tuberculosis control, hospitalization rate, medical costs, etc. of both groups were compared. *Results:* The referral rate of 90.00% and follow-up rate of 87.50% in the research group were higher than those of the control group, and the delay rate of seeing a doctor was 7.50% lower than that of the control group, $P < 0.05$; the incidence of tuberculosis in the research group was 30.00%, the rate of smear-positive tuberculosis was 20.00%, the rate of smear-negative tuberculosis was 7.50%, and the rate of new smear-positive tuberculosis rate of 2.50%, all of which were was lower than those of the control group, $P < 0.05$; the hospitalization rate of newly diagnosed tuberculosis patients in the research group was 35.00%, which was higher than that of the control group (10.00%), $P < 0.05$; the medicine expenses (1019.04 ± 62.42 yuan) and examination expenses (1687.48 ± 75.36 yuan in the research group were higher than those of the control group, $P < 0.05$. *Conclusion*: After implementing the "trinity" service, infection can be effectively prevented and controlled, and the hospitalization rate and referral follow-up rate can also be increased, but the overall medical expenses are still relatively high.

Keywords: Tuberculosis; "Trinity" service; Tuberculosis prevention and control

Online publication: September 26, 2023

1. Introduction

Tuberculosis is a high-burden disease that can affect patients' daily life and cause death. Therefore, it is extremely important to do a good job in the prevention and control of tuberculosis. China had started tuberculosis prevention and control since the 1990s, but it only applies to patients that are diagnosed with tuberculosis. Besides, the procedure for the diagnosis and the treatment for tuberculosis in village hospitals and general hospitals were rather underdeveloped, resulting in a high incidence of tuberculosis in China and increasing social security risk [1]. Therefore, in order to improve tuberculosis diagnosis and treatment, it is necessary to actively build a prevention and control system for the disease control and prevention centers,

tuberculosis designated hospitals, and grassroots medical institutions, that is, to implement the "trinity" service to reduce the risk of tuberculosis incidence. In this study, 80 newly diagnosed tuberculosis patients were treated from January 2020 to December 2022 to explore the application value of the "trinity" service.

2. Materials and methods

2.1. General information

80 newly diagnosed tuberculosis patients from January 2020 to December 2022 were selected for this study. The research group consisted of 23 males and 17 females, aged 22–68 years old, with an average of 45.16 ± 2.81 years old. The control group consisted of 24 males and 16 females, aged 23–67 years old, with an average of 45.19 ± 2.79 years old. There was no difference between the baseline data of tuberculosis patients in the research group and the control group, $P > 0.05$.

2.2. Methods

Research group ("trinity" service"): (i) A tuberculosis prevention and control system was established through the collaborative efforts of disease control centers, designated tuberculosis hospitals, and grassroots medical institutions. Among them, the disease control and prevention centers were mainly responsible for publicity and education, monitoring, and prevention and control of tuberculosis, etc.; designated hospitals were mainly responsible for inputting the patients' information, diagnosing and treating tuberculosis, and handling tuberculosis adverse reactions; primary medical institutions were mainly responsible for reporting and referral of suspected tuberculosis cases, etc., while supervising the diagnosis of tuberculosis patients. (ii) 1–2 physicians were allocated for the prevention and control of tuberculosis, with training provided; they were also responsible for liaising with other units to ensure that the patients received proper care. (iii)

Each unit carried out its designated responsibilities in accordance with the "trinity" model, enhancing the daily tuberculosis prevention and control plan and assessment framework. Only those who pass the assessment can participate in the "trinity" service. (iv) The medical institutions were supervised quarterly, in which the progress of the "trinity" service was evaluated, and problems were addressed in a timely manner. (v) Monitoring service quality: check and combine patient information, evaluate tuberculosis patient case information records, review records, and ensure tuberculosis patients receive standardized diagnosis and treatment services.

Routine tuberculosis prevention and control in the control group: after the first diagnosis of tuberculosis, the staff of the CDC (Center for Disease Control) entered the patient data, and carried out tuberculosis education to the patients, carried out prevention and control based on the guidelines for tuberculosis diagnosis and treatment, and screened the family members of tuberculosis patients. At the same time, urge patients to receive anti-tuberculosis drug treatment, and actively prescribe negative reactions, monitor the anti-tuberculosis efficacy, and record the results of sputum examination reexamination and treatment course.

2.3. Observation indicators

The referral tracking situation was compared as follows: The referral rate was calculated, indicating the percentage of suspected tuberculosis patients who received diagnosis and treatment at the nearest facility. Additionally, the tracking rate was calculated, reflecting the percentage of patients suspected of tuberculosis who could be contacted at any time to monitor their status.

The comparison of prevention and control effects involved calculating various rates, including the tuberculosis incidence rate, smear-positive tuberculosis rate (indicating positive results in sputum tuberculosis smear tests), smear-negative tuberculosis rate (indicating negative results in sputum tuberculosis smear tests),

and the new smear-positive tuberculosis rate (indicating newly discovered positive cases in sputum tuberculosis smear examinations).

The hospitalization rates of newly diagnosed tuberculosis patients in the two groups were recorded. Besides, the medical expenses were calculated, which includes examination expenses, medication expenses, and other medical expenses.

2.4. Statistical analysis

The patients' data were analyzed using SPSS 21.0. Count data and measurement data were expressed as percentages (%) and mean ± standard deviation, respectively. χ^2 test was performed for count data and *t*-test for measurement data, with $P < 0.05$ indicating statistical significance.

3. Results

3.1. Analysis of referral tracking

The research group exhibited a higher referral rate (90.00%) and follow-up rate (87.50%) compared to the control group, with a 7.50% lower rate of delayed medical consultations, and the differences were statistically significant ($P < 0.05$). Further details are shown in **Table 1**.

Table 1. Comparison of referral follow-up (%)

Group	Referral rate	Follow-up rate	Delay rate
Research group ($n = 40$)	36 (90.00)	35 (87.50)	3 (7.50)
Control group ($n = 40$)	29 (72.50)	27 (67.50)	11 (27.50)
χ^2	4.0205	4.5878	5.5411
P	0.0450	0.0322	0.0186

3.2. Analysis of tuberculosis prevention and control

In the research group, the tuberculosis incidence rate was 30.00%, the smear-positive tuberculosis rate was 20.00%, the smear-negative tuberculosis rate was 7.50%, and the new smear-positive tuberculosis rate was 7.50%. These rates were all lower than those observed in the control group ($P < 0.05$). Further details are shown in **Table 1**.

Table 2. Comparison of tuberculosis prevention and control (%)

Group	Tuberculosis incidence	Smear-positive tuberculosis rate	Smear-negative tuberculosis rate	New smear-positive tuberculosis rate
Research group ($n = 40$)	12 (30.00)	8 (20.00)	3 (7.50)	1 (2.50)
Control group ($n = 40$)	35 (87.50)	19 (47.50)	10 (25.00)	6 (15.00)
χ^2	27.2856	6.7645	4.5006	3.9139
P	0.0003	0.0093	0.0339	0.0479

3.3. Analysis of tuberculosis hospitalization

In the research group, 14 cases of newly diagnosed tuberculosis patients were hospitalized, which accounted for 35.00%. In the control group, 4 cases of newly diagnosed tuberculosis patients were hospitalized, accounting for 10.00%. The comparison of hospitalization rates between the two groups showed that the χ^2 value was 7.1685 ($P < 0.05$).

3.4. Analysis of medical expenses

The medicine expenses (1019.04 ± 62.42 yuan) and examination expenses (1687.48 ± 75.36 yuan) of the research group were higher than those of the control group ($P < 0.05$), as shown in **Table 3**.

Table 3. Comparison of medical expenses (mean ± standard deviation, yuan)

Group	Medicine expenses	Examination expenses
Research group ($n = 40$)	1019.04 ± 62.42	1687.48 ± 75.36
Control group ($n = 40$)	371.61±17.85	498.16 ± 18.49
t	103.2518	96.9380
P	0.0000	0.0000

4. Discussion

Tuberculosis prevention and control is a key task of disease prevention. With the continuous reform of the medical system, the original tuberculosis prevention and control model is no longer suitable for the current social development needs. Therefore, it is necessary to further improve the tuberculosis prevention and control strategy [2]. In this study, the "trinity" model was applied in the prevention and control of tuberculosis based on the requirements stated in the "13th Five-Year Plan," and has achieved certain results [3]. The "trinity" model represents a shift from the traditional disease prevention and control approach, wherein distinct medical institutions assume respective responsibilities for disease reporting, diagnosis and treatment, management, information entry, and tracking. This model essentially reorganizes tuberculosis prevention and control strategies according to the specific functions of each medical institution [4]. During the period of this study, the disease prevention and control centers were the core department of tuberculosis prevention and control, responsible for many tasks such as tuberculosis education, monitoring, prevention, and control; designated tuberculosis hospitals were responsible for the diagnosis and treatment of tuberculosis patients, handling adverse reactions, inputting the patients' information, etc.; grassroots medical institutions were responsible for reporting and transporting suspected tuberculosis patients, and urging confirmed tuberculosis patients to comply with medical diagnosis and treatment [5,6]. Following the implementation of the aforementioned healthcare system, it is mandatory for all organizations to designate dedicated tuberculosis diagnosis and treatment staff. Their responsibilities include effective management of confirmed tuberculosis patients, rigorous assessment, and the continuous monitoring of treatment quality. In this way, the demand for "three-in-one" service can be fulfilled and the treatment process for tuberculosis can be standardized. Besides, the "trinity" model can also optimize the resources of each medical institution, strengthen the prevention and control measures of medical institutions, thus avoiding the waste of medical resources and enhancing the quality of tuberculosis control [7].

Based on the results of this study, the referral rate (90.00%) and follow-up rate (87.50%) of the research group were higher than those of the control group; the delay rate of medical consultation of the research group was 7.50% lower than that of the control group, and the differences were statistically significant ($P < 0.05$). Therefore, it is suggested that the "trinity" mode can improve the referral and follow-up rate, and also reduces the problem of delayed treatment, making the referrals and treatment more effective. This is because the "trinity" model facilitates the registration and reporting of tuberculosis patients at primary medical centers. It helps patients complete clinical diagnosis and treatment while maximizing the role of primary medical institutions. This encourages tuberculosis patients to seek timely diagnosis and treatment, effectively contributing to tuberculosis prevention and control efforts [8]. Another set of data showed that the tuberculosis incidence

rate of 30.00%, smear-positive tuberculosis rate of 20.00%, smear-negative tuberculosis rate of 7.50%, and new smear-positive tuberculosis rate of 2.50% in the research group, which were all significantly lower than those of the control group ($P < 0.05$). Therefore, it is suggested that the "trinity" model can reduce the risk of tuberculosis. This the "trinity" model includes training the personnel of various medical institutions, optimizing the allocation of medical resources, and assigning special personnel to supervise the diagnosis and treatment of tuberculosis. All of these ensure that the patients can receive proper care, making tuberculosis prevention and control more effective [9]. In addition, encouraging grass-roots hospitals to participate in tuberculosis prevention and control and setting up designated tuberculosis diagnosis and treatment institutions has the following effects: it can ensure that TB patients can receive high-quality medical services, and it can also enhance the compliance of tuberculosis patients with diagnosis and treatment, thereby increasing the detection rate of tuberculosis. Systematic prevention and control strategies and early diagnosis and treatment of suspected tuberculosis pathology can reduce the rate of newly diagnosed tuberculosis patients. The results of this study also showed that the hospitalization rate of newly diagnosed tuberculosis patients in the research group was 35.00% higher than that the control group (10.00%), with statistical significance ($P < 0.05$). However, the medicine expenses (1019.04 ± 62.42 yuan) and examination expenses (1687.48 ± 75.36 yuan) were higher than those of the control group ($P < 0.05$). It is suggested that the "trinity" model can increase the hospitalization rate of newly diagnosed pulmonary tuberculosis patients, but the overall medical expenses was also higher. This is because the "trinity" model provides convenient medical services for newly diagnosed tuberculosis patients, so suspected cases could be hospitalized easily. Medical insurance policies also contributed to reducing the financial burden of the patients, therefore increasing the hospitalization rate. However, as excellent diagnosis and treatment environment was provided for the patients with the "trinity" model, and that medical intervention was provided immediately after abnormalities were detected, so the medical expenses were slightly higher. This indicates that the "trinity" service still has certain limitations and requires further improvements [10]. Furthermore, in the practical execution of the "trinity" service, it is crucial to ignite the enthusiasm of personnel across different medical institutions. Besides, it is crucial to optimize the tuberculosis treatment model and promptly address any adverse reactions experienced by patients to enhance patient compliance. Additionally, improving the conditions for sputum tuberculosis smear examinations is essential to ensure the accuracy of the tests.

5. Conclusion

In summary, the "trinity" model plays a crucial role in tuberculosis prevention and control. It helps track newly diagnosed tuberculosis patients promptly, provides timely medical intervention for suspected cases, ultimately reducing the risk of tuberculosis transmission, increasing patient hospitalization rates, and bolstering the effectiveness of prevention and control efforts. Nevertheless, there is a pressing need to refine the "trinity" service strategy in clinical practice due to the high medical expenses associated with it.

Disclosure statement

The author declares no conflicts of interest.

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Oncology Treatment Discovery, 2023, Volume 1, Issue 2
http://ojs.bbwpublisher.com/index.php/OTD

Analysis of the Clinical Efficacy of Buzhong Yiqi Decoction in the Treatment of Mild COVID-19

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Abstract: *Objective:* To explore the clinical significance of Buzhong Yiqi decoction in treating patients with mild COVID-19. *Methods:* 88 patients with mild COVID-19 admitted to the hospital for outpatient treatment from December 2022 to July 2023 were selected as the research subjects. They were divided into two groups through random number generator. The control group was given conventional Western medicine treatment, while the observation group was given Buzhong Yiqi decoction combined treatment. The effects of the two types of treatment were compared and analyzed. *Results:* Before treatment, there was no difference in inflammatory indicators between the two groups ($P > 0.05$); after treatment, the C-reactive protein (CRP), white blood cells (WBC), and interleukin-6 (IL-6) levels of the observation group were lower than those of the control group ($P < 0.05$). The treatment received in the observation group was significantly more effective the treatment received in the control group ($P < 0.05$). There was no difference in the scores of the traditional Chinese medicine syndrome scale between the two groups before treatment ($P > 0.05$). The scores for fatigue, sputum, cough, and fever of the observation group after treatment were all lower than those of the control group ($P < 0.05$). However, there was no statistically significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$). *Conclusion:* Buzhong Yiqi Decoction can reduce symptoms and improve the body's inflammatory response of patients with mild COVID-19 patients.

Keywords: Novel coronavirus pneumonia; Buzhong Yiqi decoction; TCM syndrome scale; Inflammatory factors

Online publication: September 26, 2023

1. Introduction

Coronavirus Disease 2019 (COVID-19) is an acute infectious disease of the respiratory tract that is caused by the SARS-CoV-2 virus [1,2]. This virus is transmitted through close contact and respiratory droplets and it is highly contagious. Its symptoms include dry cough, fatigue, and fever. Some patients may experience gastrointestinal symptoms and symptoms such as muscle aches, sore throat, runny nose, and nasal congestion. Hypoxemia, dyspnea or multiple organ failure, bleeding and coagulopathy, uncorrectable metabolic acidosis, and sepsis may also occur as the condition worsens. In severe cases, it may lead to shock and acute respiratory distress, which are life-threatening [3]. Studies have found that patients with mild COVID-19 generally have no symptoms of pneumonia and usually only experience mild fatigue and mild fever. Most patients have a good

prognosis, while some have more severe after effects, especially those with underlying diseases or older patients [4]. COVID-19 can be divided into 4 levels of severity: critical, severe, ordinary, and mild. Western medical treatment involves the use of antibacterial drugs, antiviral, oxygen therapy, and supportive therapy. If the patient is critically ill, treatment options such as immunotherapy, blood purification treatment, convalescent plasma treatment, renal replacement therapy, circulatory support, and respiratory support are employed. In contrast, traditional Chinese medicine (TCM) treatment involves using Chinese patent medicines such as Xuebijing injections or decoctions such as Qingfei Paidu decoction and Buzhong Yiqi decoction, which are all proven effective [5]. Therefore, in this study, the effect of Buzhong Yiqi Decoction in treating mild patients with new coronavirus pneumonia was analyzed.

2. Materials and methods

2.1. General information

In this study, 88 patients with mild COVID-19 that admitted to the hospital for outpatient treatment from December 2022 to July 2023 were selected for this study. They were divided into two groups through a random number generator, with 44 patients in each group. The ages of the patients in the control group ranged from 20 to 65 years old, with an average of 42.3 ± 6.1 years, including 18 females and 26 males. The ages of the patients in the observation group ranged from 22 to 67 years old, with an average of 42.5 ± 6.2 years, including 17 females and 27 males.

Inclusion criteria: (1) Patients with varying degrees of respiratory symptoms and fever that are consistent with the "COVID-19 Diagnosis and Treatment Plan (Trial Version 6)" [6] and the "Shanghai TCM Diagnosis and Treatment Plan for COVID-19; (2) patients who met the relevant standards in "Trial Implementation" [7]; (2) Patients who were ≥18 years old; (3) patients who were conscious and could communicate normally. Exclusion criteria: (1) Children or pregnant women; (2) patients with severe organ diseases such as heart, liver, and kidney disease; (3) patients with Alzheimer's disease, mental illness, autoimmune diseases, and malignant tumors; (4) patients who dropped out of the study or had incomplete data.

There was no difference in data between the two groups ($P > 0.05$), indicating comparability.

2.2. Method

2.2.1. Control group

The patients of the control group underwent conventional Western medicine treatment, which included resting, formulating a diet plan, sufficient caloric intake, and the oral administration of 200mg Arbidol (three times/d). The treatment lasted for seven days.

2.2.2. Observation group

Based on the above treatment, the observation group was treated with Buzhong Yiqi decoction. The essential prescriptions were as follows: 3 g each of Bupleurum, Cimicifuga, *Angelicae sinensis*, tangerine peel, fried Atractylodes, and ginseng; 5 g of roasted licorice, 10 g of honey-roasted Astragalus. The amount of each ingredient can be increased or decreased according to symptoms. If the patient had yin deficiency and lung dryness, 15 g each of Lily and *Rehmannia glutinosa* were added. If the patient had phlegm-heat stagnation in the lungs, 15 g Trichosanthes were added. The ingredients were decocted in cold water, and 200 mL of the decoction were extracted and consumed, 100 mL/time, two times/d – once in the morning and once in the evening for seven days.

2.3. Observation indicators

(1) Inflammation indicators: 3 mL of cubital venous blood were collected. The blood samples were centrifuged for 10 minutes at 3000 r/min, the upper serum was extracted for analysis. The C-reactive protein (CRP) using conventional methods, and the white blood cell count (WBC) and interleukin-6 (IL-6) were measured; (2) Based on the "Guiding Principles for Clinical Research of New Traditional Chinese Medicines (Trial)" [8], a TCM syndrome scale was established, including fatigue, sputum, cough, and fever; the scores for each item ranged from 0–4 points depending on the severity of the symptoms. 3 points were given for severe symptoms, 2 points for moderate symptoms, 1 point for mild symptoms, and 0 for none. (3) During the treatment period, the adverse reactions of the two groups were recorded, including diarrhea, loss of appetite, and stomach pain.

2.4. Criteria for judging efficacy

The patients were considered fully recovered when two throat swab tests were negative, and there were no symptoms such as diarrhea, headache, dyspnea, or fever in the last three days [9].

2.5. Statistical analysis

χ^2 and *t*-tests were used to compare count data and measurement data between the two groups. $P < 0.05$ was used to indicate statistical significance.

3. Results

3.1. Comparison of cure rates between the two groups

After seven days of treatment, 40 patients in the observation group fully recovered, with a cure rate of 90.91% (40/44); while 30 cases in the control group fully recovered, with a cure rate of 68.18% (30/44). The difference between the cure rates of the two groups were statistically significant ($P < 0.05$).

3.2. Changes in inflammatory factors in the two groups before and after treatment

There was no difference in inflammatory factor indicators between the two groups before treatment ($P > 0.05$); IL-6, CRP, and WBC in the observation group were all lower than those in the control group after treatment ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of inflammatory factors between the two groups (mean ± standard deviation)

Group	CRP (mg/L)		WBC ($\times 10^9$/L)		IL-6 (ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group ($n = 44$)	4.67 ± 1.55	2.73 ± 1.18	16.28 ± 3.82	9.34 ± 2.02	110.36 ± 22.74	54.28 ± 12.02
Observation group ($n = 44$)	4.69 ± 1.57	1.32 ± 0.44	16.93 ± 3.67	5.02 ± 2.18	110.87 ± 21.75	32.45 ± 11.81
t	0.664	9.053	1.197	5.287	0.753	6.228
P	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05

3.3. Changes in TCM syndrome scores before and after treatment in the two groups

Before treatment, there was no difference in the scores between the two groups ($P > 0.05$); after treatment, compared with the control group, the fatigue, sputum expectoration, fever, and cough scores of the observation group all decreased, and the comparison between the groups was statistically significant ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of TCM syndrome scores between the two groups (mean ± standard deviation, points)

Group	Weakness		Expectoration		Cough		Fever	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 44)	1.28 ± 0.73	0.68 ± 0.31	1.17 ± 0.43	0.45 ± 0.11	2.67 ± 0.84	0.92 ± 0.33	1.38 ± 0.54	0.83 ± 0.24
Observation group (n = 44)	1.31 ± 0.74	0.17 ± 0.22	1.19 ± 0.55	0.02 ± 0.14	2.69 ± 0.82	0.59 ± 0.23	1.41 ± 0.57	0.11 ± 0.15
t	0.764	9.266	1.083	6.383	0.912	6.112	0.254	7.365
P	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05

3.4. Comparison of adverse reactions between the two groups

Adverse reactions such as diarrhea and loss of appetite occurred during the treatment in both groups, with no statistical differences in the incidence rates ($P > 0.05$), as shown in **Table 3**.

Table 3. Comparison of adverse reactions between the two groups (n [%])

Group	Diarrhea	Decreased appetite	Stomachache	Incidence rate
Control group (n = 44)	2 (4.55)	3(6.82)	2 (4.55)	7 (15.91)
Observation group (n = 44)	1 (2.27)	2 (4.55)	1 (2.27)	4 (9.09)
χ^2 value				0.654
P				> 0.05

4. Discussion

As a highly contagious respiratory disease, COVID-19 spreads through fecal-oral, aerosol, close contact, and respiratory droplets. It can affect the kidneys, gallbladder, liver, and heart, so as the spleen and lungs. However, the pathological changes are different for each patient, and their clinical manifestations are also somewhat different. Its symptoms are mainly fatigue, dry cough, and fever. Besides, it has an incubation period of 1–14 days [10]. In TCM, the lungs are considered the leading disease site for COVID-19. Its pathogenesis characteristics include blood stasis, poison, heat, and dampness because a spleen and stomach deficiency can lead to insufficient lung qi, and the lungs are the foundation of qi. Deficiency of the spleen will lead to the invasion of external evils, so treatment follows the basic principles of dispersing cold, relieving the surface, removing blood stasis, and removing dampness [11,12]. Buzhong Yiqi decoction was used in this study, which composed of angelica, bupleurum, dried tangerine peel, cohosh, astragalus, roasted licorice, ginseng, and fried Atractylodes. Among them, astragalus is the king medicine with anti-fatigue, toxin-supporting properties as it strengthens the muscles and the immune system. Ginseng can restore pulse, strengthen the pulse and replenish vitality. Stir-fried Atractylodes has the effect of antiperspirant, removing dampness and diuresis, nourishing qi, and strengthening the spleen. Tangerine peel can remove dampness and phlegm, regulate qi, and strengthen the spleen. Cimicifugae Rhizoma can clear away heat and has a detoxification effect, and it also replenishes qi and yang. Bupleurum has the effects of nourishing yang, reducing fever, soothing the liver and relieving depression. prepared licorice can harmonize various medicines and provide a comprehensive prescription [13,14]. Together, they have the effects of nourishing qi and blood, replenishing qi, relieving cough, and eliminating phlegm. At the same time, modern pharmacological research showed that the active ingredients of ginseng, Atractylodes, and Astragalus can enhance the phagocytosis of viruses and bacteria by the reticuloendothelial system and

monocyte-macrophages and improve human immune function. In particular, *Astragalus* has a two-way regulatory effect, in which it can reduce the level of inflammatory factors in the body, alleviate inflammation, improve the body's internal environment, and restore bodily functions [15].

In summary, Buzhong Yiqi Decoction can reduce the body's inflammatory response, improve symptoms, and improve the treatment effect of mild COVID-19 patients. It also does not increase the rate adverse reactions. Therefore, this treatment method is safe and should be popularized.

Disclosure statement

The author declares on conflict of interest.

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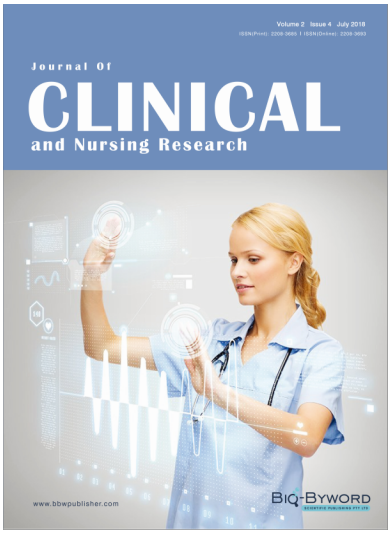

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